

# **EXHIBIT A81**

# Correspondence

## Brexit threatens biosecurity

Biosecurity is likely to be seriously compromised by the United Kingdom's exit from the European Union. Common rules and safeguards, backed by a common judicial system, have for decades protected human, animal and plant health against biological hazards. Even so, ash dieback still threatens 60 million UK trees, and African swine fever has spread to Europe (see I. Capua and M. Monti *Nature* **566**, 326; 2019).

Despite the rush to pass the huge volume of secondary legislation required by the EU Withdrawal Act before the end of this month, it is almost certain that the mechanisms and operational capacities to replicate these protective systems nationally will not be in place (see, for example, [go.nature.com/2tislyv](http://go.nature.com/2tislyv)). Establishing such mechanisms will take time — and, meanwhile, hazards will persist.

Although we might still exchange information with the EU in response to common threats, we shall no longer be able to access the relevant data systems. Even if we continue to collaborate in research and innovation, our contribution to biological security policies will dwindle. Our voice in strategic decision-making will be silenced.

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*\*On behalf of 4 correspondents (see [go.nature.com/2u2jswz](http://go.nature.com/2u2jswz) for full list.)*  
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## Fluorochemicals: make polluters pay

Who should bear the huge cost of cleaning up pollution by fluorochemicals (see *Nature* **566**, 26–29; 2019)? For example, the cost of ridding US military bases of these chemicals in fire-fighting foams is likely to top US\$2 billion (see [go.nature.com/2w5qjyt](http://go.nature.com/2w5qjyt)).

In our view, it is time to invoke the ‘polluter pays’ principle and

make companies responsible for the true costs of their chemical products. As noted by the United Nations Environment Programme, “The vast majority of human health costs linked to chemicals production, consumption and disposal are not borne by chemicals producers, or shared down the value-chain” (see [go.nature.com/2wonrvy](http://go.nature.com/2wonrvy)).

Such costs should not be borne by taxpayers, the state or national treasury or by any other third party (see [go.nature.com/2xzahnh](http://go.nature.com/2xzahnh)). Rather, they should be met by producer industries to avoid market distortion.

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## Retiring significance: a free pass to bias

Statistical significance sets a convenient obstacle to unfounded claims. In my view, removing the obstacle (V. Amrhein *et al.* *Nature* **567**, 305–307; 2019) could promote bias. Irrefutable nonsense would rule.

More stringent thresholds of significance are needed for most fields, which currently assume statistical significance when  $P$  values are less than 0.05 (see, for example, D. J. Benjamin *et al.* *Nature Hum. Behav.* **2**, 6–10; 2018; J. P. A. Ioannidis *J. Am. Med. Assoc.* **319**, 1429–1430; 2018).

Dichotomous conclusions can be useful for pinning down discoveries of gene variants for osteoporosis, new bosons or carcinogens, say. But focusing on effect sizes can often be better than determining whether an effect exists. That said, I find the “compatibility interval” proposed by Valentin Amrhein *et al.* potentially confusing — and biases could render the entire interval incompatible with truth.

If rules are set before data collection and analysis, then statistical guidance that is based on appropriate thresholds is helpful. However, post hoc and subjective statistical inference is susceptible to conflicts of interest.

A company could, for example, claim that any results somehow support licensing of its product.

Careful thinking before a study starts should pick the best, fit-for-purpose statistical inference tool and pre-specify the rules of the game — whether frequentist, Bayesian or other. So, although the obstacle of statistical significance can be surmounted by trickery, removing it altogether is worse.

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## Retiring significance: raise the bar

In my view, the proposal to retire statistical significance conflates two problems (V. Amrhein *et al.* *Nature* **567**, 305–307; 2019). These should be addressed separately.

One problem is the value of having a term that signifies whether an experiment provides evidence of an effect — that is, it achieves ‘statistical significance’.

The second problem involves defining statistical significance as, say,  $P < 0.05$ . Many scientists object to this threshold because it can prevent publication of experiments when  $P > 0.05$  (see, for example, D. Lakens *et al.* *Nature Hum. Behav.* **2**, 168–171; 2018). I have the opposite concern. Careful analysis of  $P$  values close to 0.05 shows that they don’t provide evidence for a genuine association (D. J. Benjamin *et al.* *Nature Hum. Behav.* **2**, 6–10; 2018). Instead, they provide evidence supporting the null hypothesis of no association.

By focusing on the term ‘statistical significance’, we ignore the more important issue of what constitutes sufficient evidence of a true association. Let’s have that

discussion and redefine what we mean by a statistically significant finding.

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## Retiring significance: keep hypothesis tests

We agree that arbitrarily branding experimental findings as significant or non-significant generates a false sense of certainty (V. Amrhein *et al.* *Nature* **567**, 305–307; 2019). However, when done properly, hypothesis testing is an important precondition for estimating an effect size.

In his 1928 book *Statistical Methods for Research Workers*, British statistician Ronald Fisher remarked that “it is a useful preliminary before making a statistical estimate ... to test if there is anything to justify estimation at all”. And British polymath Harold Jeffreys declared in *Theory of Probability* in 1939 that “variation must be taken as random until there is positive evidence to the contrary”. Hence, testing and estimation are complementary. Testing establishes whether there is an effect, and that helps to determine whether or not the magnitude needs to be estimated.

What happens when statistical testing is skipped and the null hypothesis is ignored? Well, noise would be interpreted as structural, and any differences between observations would be considered meaningful. Parameters would need to be estimated for all these differences, resulting in a “mere catalogue” of data “without any summaries at all”, as Jeffreys put it.

Without the restraint provided by testing, an estimation-only approach will lead to overfitting of research results, poor predictions and overconfident claims.

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